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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/360,685	07/26/1999	ANTONELLO COVACCI	CHIR-0157	4520

27476 7590 11/01/2002

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EXAMINER
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ART UNIT	PAPER NUMBER
1645	25

DATE MAILED: 11/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/360,685	Covacci et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 25, 2002*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *40, 41, 45, 47, 54, 56, 57, 59, 62, 63, 68, 70, 72, 75, 76, 78, 80* is/are pending in the application. (80-139)

4a) Of the above, claim(s) *81, 84-123, and 126-139* is/are withdrawn from consideration.

5) ☒ Claim(s) *40, 41, and 72* is/are allowed.

6) ☒ Claim(s) *45, 47, 54, 56, 57, 59, 62, 63, 68, 70, 75, 76, 78, 80, 82, 83, 124, 125* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *32.*
4) ☒ Interview Summary (PTO-413) Paper No(s). *34.*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 07/25/02 (paper no. 29) in response to the non-final Office Action mailed 02/28/02 (paper no. 28). With this, Applicants have amended the specification.

Status of Claims

2) Claims 38, 39, 42, 44, 48, 50, 51, 53, 60, 61, 64-66, 71, 73, 74, 77 and 79 have been canceled via the amendment filed 07/25/02.

Claims 40, 45, 47, 54, 56, 57, 59, 62, 63, 70, 75, 76, 78 and 80 have been amended via the amendment filed 07/25/02.

New claims 81-139 have been added via the amendment filed 07/25/02.

Claims 40, 41, 45, 47, 54, 56, 57, 59, 62, 63, 68, 70, 72, 75, 76, 78 and 80-139 are pending.

New claims 81, 84-123 and 126-139 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 40, 41, 45, 47, 54, 56, 57, 62, 63, 68, 70, 72, 75, 76, 78, 80 and new claims 82, 83, 124 and 125 encompassing the elected invention, are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' information disclosure statement filed 09/16/02 (paper no. 32). The information referred to therein has been considered and a signed copy of the same is attached to this Office Action (paper no. 34).

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the drawings made in the Office Action mailed 02/14/00 (paper no. 3) under 37 C.F.R.1.84 is withdrawn in light of Applicants' submission of the formal drawings. These formal drawings have been approved by the Draftsperson.

7) The objection to the specification made in paragraph 11(a) of the Office Action mailed 02/28/02 (paper no. 28) is withdrawn in light of Applicants' amendment to the specification.

8) The objection to the specification made in paragraph 11(b) of the Office Action mailed 02/28/02 (paper no. 28) is withdrawn in light of Applicants' amendment to the specification.

9) The objection to the specification made in paragraph 11(c) of the Office Action mailed 02/28/02 (paper no. 28) is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Moot

10) The rejection of claim 60 made in paragraph 15(b) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

11) The rejection of claims 42, 48, 51, 61, 73, 77 and 79 made in paragraph 15(c) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 44, 50, 53, 66 and 74 made in paragraph 15(d) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

13) The rejection of claims 48, 50, 51, 53, 61, 73, 74, 77 and 79 made in paragraph 17 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the claims.

14) The rejection of claims 38, 42 and 44 made in paragraph 19 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C § 102 (b) as being anticipated by Hirschl *et al.* (*In*: *Helicobacter pylori, Gastritis and Peptic Ulcer*. (Ed) Malfortheiner *et al.* Springer-Verlag Berlin, pages 141-146, 1990), is moot in light of Applicants' cancellation of the claims.

15) The rejection of claims 38, 39, 42, 44, 48, 50, 60, 66, 71, 73, 74, 77 and 79 made in

paragraph 20 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C § 102(b) as being anticipated by Clayton *et al.* (*In*: *Helicobacter pylori, Gastritis and Peptic Ulcer*. (Eds) Malfertheiner *et al.* Springer-Verlag, Berlin, pages 167-171, 1990), is moot in light of Applicants' cancellation of the claims.

16) The rejection of claims 38, 39, 42, 44, 71, 73 and 74 made in paragraph 21 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C § 103(a) as being unpatentable over, Tummuru *et al.* (*In*: Abstracts of the 91st General Meeting of the American Society for Microbiology, Dallas, Texas, 5-9 May 1991, abstract B-127), is moot in light of Applicants' cancellation of the claims.

17) The rejection of claims 60 and 77 made in paragraph 22 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C § 103(a) as being unpatentable over Clayton *et al.* (*In*: *Helicobacter pylori, Gastritis and Peptic Ulcer*. (Eds) Malfertheiner *et al.* Springer-Verlag, Berlin, pages 167-171, 1990), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

18) The rejection of claim 40 made in paragraph 15(a) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

19) The rejection of claim 62 made in paragraph 15(b) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

20) The rejection of claims 45, 54, 62, 63, 75 and 78 made in paragraph 15(c) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

21) The rejection of claims 41, 47, 56, 57, 59, 68, 76 and 80 made in paragraph 15(d) of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim(s).

22) The rejection of claims 45, 54, 62, 68, 75 and 78 made in paragraph 16 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, first paragraph, as containing new

matter, is withdrawn in light of Applicants' arguments.

Rejection(s) Maintained

23) The rejection of claims 45, 47, 48, 54, 56, 57, 59, 62, 63, 68, 70, 75, 76, 78 and 80 made in paragraph 17 of the Office Action mailed 02/28/02 (paper no. 28) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is maintained for reasons set forth therein and herebelow.

New claims 82, 83, 124 and 125 are now included in this rejection.

Applicants' arguments have been carefully considered, but are non-persuasive.

Applicants acknowledge that the enablement requirement mandates the specification to teach those in the art how to make and use the claimed invention without undue experimentation. Applicants contend that the enablement requirement of 35 U.S.C. § 112, first paragraph, is satisfied if a disclosure contains sufficient information such that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. Applicants cite case law and state that the test of enablement is not whether any experimentation is necessary, but that if experimentation is necessary, it is undue. Applicants assert that any conclusion of non-enablement must be based on the evidence as a whole. Applicants state that the present invention is defined by claims directed to a purified polypeptide of the amino acid sequence, SEQ ID NO: 5, and 'fragments' thereof, vaccines containing the same, and methods of preparing the same. Applicants allege that the Office has not established a *prima facie* case of non-enablement. Applicants submit that the skilled artisan would be able to make and use the claimed invention "using the application as a guide". Applicants assert that the specification need only disclose 'one' method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims to satisfy the enablement requirement. Applicants submit that an extended period of experimentation may not be undue if the skilled artisan is "given sufficient direction or guidance". With regard to the recited polypeptides having substantial noncytotoxicity, Applicants state that the specification at page 50 discloses a representative example in which the cytotoxicity of CAI antigen was determined by measuring the vacuolizing activity of the polypeptide on HeLa cells. Applicants assert that using the "application as a guide" one of ordinary skill in the art would have been able to determine which polypeptide fragments are 'substantially noncytotoxic'. Applicants dismiss Oderda's teaching of strong association of the

full length CAI antigen with cytotoxicity and state that this is not to say that the CAI antigen is cytotoxic. With regard to the teachings of McGuinnes *et al.*, Applicants state that enablement does not require 100% success. Applicants cite Manetti *et al.* (*Infect. Immun.* 63 (11): 4476-4480, 1995) as reporting that administration of cytotoxin protein to rabbits effectively induces a 'neutralizing' response.

However, contrary to Applicants' assertion, Applicants have not disclosed even one method for making and using the full length CAI, CT or HSP (let alone fragments as recited) that is 'substantially noncytotoxic', immunogenic, *H. pylori*-specific and being capable of serving as a therapeutic and prophylactic vaccine. The instant specification fails to provide 'sufficient direction or guidance" to reproducibly practice the invention as claimed. As clearly set forth in paragraph 17 of the Office Action mailed 02/28/02 (paper no. 28), the instant specification does not meet the enablement provisions of 35 U.S.C. § 112, first paragraph. The CAI antigen is known in the art to be associated with cytotoxicity. Contrary to Applicants' assertion, the instant specification does not serve as a 'guide' enabling one of skill in the art to produce a non-fragmented whole CAI, CT or HSP antigen of *H. pylori* that possesses the following required functions: a) substantial non-cytotoxicity; b) ability to induce antibodies specific to *H. pylori*; c) ability to serve as a prophylactic or therapeutic vaccine either alone or in combination. Contrary to Applicant's contention, the instant application does not serve as a 'guide' to identify and then produce even a single full length CAI, CT or HSP polypeptide, or a single 10-mer or 15-mer thereof (let alone a representative number), which fragment has the three required functions. How to determine whether or not one or more of the recited antigen(s) is 'substantially noncytotoxic' is not described. What degree of cytotoxicity or noncytotoxicity qualifies as 'substantial noncytoxicity' is not taught. Contrary to Applicants' contention, the disclosure on page 50 of the instant specification is limited only to the statement that some strains of *H. pylori* show vacuolizing activity on HeLa cells while the activity was absent in other strains. This merely indicates that some strains of *H. pylori* produce an antigen having vacuolizing activity on HeLa cells whereas other strains do not. However, this statement does not enable either a full length CAI antigen or a fragment (let alone a representative number of fragments) of the CAI antigen as a substantially noncytotoxic immunogen capable at the same time of inducing *H. pylori*-specific

antibodies and serving as a prophylactic or therapeutic vaccine. This part of the specification in fact teaches the variability in the CAI antigen among different strains of *H. pylori*. This variability factor emphasizes how one of skill in the art would have had to engage in considerable quantity of undue experimentation to reproducibly practice the invention as claimed.

Clearly, having the instant disclosure before them, those skilled in the art would not have been able to make and use the invention as claimed. The only recitation/description for CAI, CT or HSP antigen or an "at least 10" or "at least 15" amino acid-long fragment thereof concurrently having the ability to induce the production of antibodies to *H. pylori* and exhibiting substantial noncytotoxicity was present exclusively in some claims, as originally presented. The antecedence for these recitations was provided in the instant specification via the amendment filed 08/07/00 by inserting these recitations at page 4 of the specification. Other than this brief mentioning, there is no teaching or specific guidance/direction within the instant specification as to how to reproducibly produce such 'at least' 10-mer or 15-mer fragments of CAI, CT or HSP antigen of *H. pylori* such that the fragments have the concurrent ability to induce the production of antibodies to *H. pylori*, the ability to exhibit substantial noncytotoxicity and the ability to serve as a prophylactic and therapeutic vaccine. The instantly claimed SEQ ID NO: 5 is 1147 amino acid residues-long. The instantly recited heat shock protein and CT are also more than 1000 amino acid residues-long. See Figures. A myriad of 'at least' 10-mer or 15-mer polypeptide fragments of SEQ ID NO: 5, heat shock protein, or CT antigen are encompassed in the scope of the claims. An "at least" 10-mer or an "at least 15-mer" polypeptide fragments encompass innumerable numbers of polypeptide species that are 10, 12, 13, 14, 15, 6, 17, 18, 19, 20, 21, 25, 30, 35, 42, etc. amino acid-residues long, substantially noncytotoxic, immunogenic, *H. pylori*-specific and capable of serving as a prophylactic or therapeutic vaccine. Not even a single such fragment, let alone a representative number of such at least 10-mer or 15-mer polypeptides of CAI, CT or HSP having the required associated functions of: a) substantial noncytotoxicity; b) ability to induce antibodies specific to *H. pylori*, and c) ability to serve as a prophylactic or therapeutic vaccine, is enabled. Although producing a myriad of such polypeptide fragments may be well within the realm of routine experimentation, obtaining such polypeptides or their fragments that necessarily have the required/recited functions requires considerable quantity of complex and time consuming

experimentation that is undue. How to make such polypeptide fragments such that they also possess the required functional properties is not taught. Which exact parts of the native SEQ ID NO: 5 (CAI), CT or HSP contributes to cytotoxicity or substantial noncytotoxicity has not been taught so that one skilled in the art can produce a polypeptide or its fragment that is noncytotoxic, immunogenic and *H. pylori*-specific at the same time. Due to the art-recognized antigenic variability among different strains of *Helicobacter pylori*, one skilled in the art cannot predict, envision and produce, without undue experimentation, a CAI, CT or HSP polypeptide or fragments thereof as claimed, that are substantially noncytotoxic, immunogenic, *H. pylori*-specific and capable of serving as a therapeutic or prophylactic vaccine.

The *Helicobacter pylori* CT claimed in the instant claims encompasses both recombinant and non-recombinant CT. Claim 70 requires that the at least ten amino acid-containing *Helicobacter pylori* cytotoxin (CT) protein has the ability to induce the production of antibodies to '*Helicobacter pylori*'. However, it is known in the art that all isolates of *Helicobacter pylori* do not produce CT and therefore any 10-mer CT fragment would not be able to induce antibodies to the generically recited '*Helicobacter pylori*' as broadly recited. Furthermore, from the state of the art it appears that one cannot predict any full length *Helicobacter pylori* CT to be capable of eliciting neutralizing antibodies to '*Helicobacter pylori*'. For instance, the reference of Manetti *et al.* (*Infect. Immun.* 63: 4476-4480, November 1995) submitted by Applicants demonstrated that a recombinant CT protein "lacked any biological activity" and failed to induce antibodies that are neutralizing. This teaching indicates that a 10-mer or 15-mer fragment of such a recombinant *H. pylori* CT protein would be unlikely to have the ability to induce useful antibodies to *Helicobacter pylori* and is unlikely to serve as a fragment suitable for use as a prophylactic or therapeutic vaccine. Furthermore, Manetti *et al.* taught that epitopes of *Helicobacter pylori* CT that induce neutralizing antibodies are conformational (see abstract of Manetti *et al.*). Absent a showing, there is no guarantee that a 10-amino acid long or 15-amino acid long CT would maintain such critically important conformational epitopes and would serve as a prophylactic or therapeutic vaccine.

With regard to the recitation of prophylactic or therapeutic vaccines, Applicants cite case law and contend that compliance with the enablement requirement does not turn on whether an

example is disclosed. Applicants assert that the application need not contain an example if the invention is 'otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue experimentation'. Applicants point to MPEP § 2107.03 and state that Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials, and that it is improper for Office personnel to request regarding the degree of effectiveness in humans. However, it should be noted that Applicants were not required to provide evidence by the Office regarding the degree of effectiveness in humans. Since a patent application claiming one or more polypeptides or polypeptide fragments as components of a 'prophylactic' or 'therapeutic' vaccine has to necessarily show either *in vivo* protective ability of the claimed product, **or** *in vitro* assay results that correlate with *in vivo* protective efficacy of the claimed product, the following statement was made in paragraph 17 of the Office Action mailed 02/28/02 (paper no. 28):

> The line bridging pages 38 and 29 describes that the instantly claimed vaccine may either be "prophylactic (to prevent infection) or therapeutic (to treat disease after infection)". Therefore, the claimed prophylactic vaccine should prevent *H. pylori* infection when administered before a subject acquires the infection, and the claimed therapeutic vaccine should have the capacity to treat *H. pylori* infection when administered after a subject acquires the infection. The instant specification on page 50, lines 15 and 16 indicates that the non-recombinant CAI polypeptide was used to immunize rabbits. However, ten amino acid- or fifteen amino acid-long fragments of the claimed CAI polypeptide, let alone the second polypeptide CT or HSP, are neither enabled as a prophylactic vaccine capable of preventing *H. pylori* infection, nor as a therapeutic vaccine capable of treating an already existing *H. pylori* infection. The instant specification lacks any animal **or** human data or evidence demonstrating the prophylactic or therapeutic efficacy of the claimed vaccine with or without the second polypeptide, **or** any serological evidence that is predictive of or correlative with prophylactic and therapeutic efficacy of the vaccine. Without an enabling disclosure and a concrete demonstration that the claimed polypeptide, especially any fragment comprising at least 10 or 15 amino acid residues, prevents a *H. pylori* infection, or treat an already existing *H. pylori* infection, with or without added homologous or heterologous antigens (CT or HSP), one of ordinary skill in the art cannot practice the invention as claimed. This is particularly important because the prophylactic or therapeutic efficacy of any 10-mer or 15-mer bacterial polypeptide antigen fragment is not a predictable event. ..... Whether or not such products have functional or biologic capacity to be immunogenic, prophylactic and therapeutic is unknown and unpredictable, and would have required undue experimentation. The same holds true with respect to the second polypeptide, HSP or CT.
>
> Furthermore, the *Helicobacter pylori* HSP is known to and is described in the specification to be highly homologous with the HSP of all living organisms, including animals (see page 7 and 60). Induction of antibodies to such a molecule contained in a vaccine would potentially induce antibodies that can produce pathologic autoimmune consequences. A vaccine comprising such potentially autoimmune polypeptides cannot be viewed as a 'prophylactic' or a 'therapeutic' vaccine. Since which 10-mer or 15-mer fragment would retain *H. pylori* specificity and serve as a prophylactic or therapeutic vaccine against *H. pylori* infection while at the same time not produce harmful autoimmune antibodies against host tissues is neither disclosed, nor could be predicted and since the epitopes on the HSP responsible for therapeutic or prophylactic properties are not known or identified, one of ordinary skill would be forced into experimentation that is undue.

The instant specification clearly lacks either clinical or nonclinical, and *in vitro* or *in vivo* evidence to show that the claimed polypeptide(s) or fragments thereof as recited, are capable of serving as prophylactic or therapeutic vaccines. Applicants acknowledge that enablement requires that the application teach how to make and use the invention without undue experimentation, but assert that one having ordinary skill in the art would be able to make and use the invention without undue experimentation 'using only the application as a guide'. However, if one skilled in the art used the instant application as a 'guide', one would have been successful in making and using a CAI antigen of *H. pylori* that is cytotoxic or vacuolizing on HeLa cells. See last paragraph on page 50. Applicants admit that the specification at page 38 teaches that each of the *H. pylori* proteins disclosed "may be" used as a sole vaccine candidate or in combination with one or more other antigens. However, a mere speculative statement that a bacterial protein that is cytotoxic or that is associated with cytotoxicty "may be" used as a vaccine is insufficient to meet the enablement provisions of 35 U.S.C. § 112, first paragraph. Applicants assert that the specification discloses a full length CAI antigen protein used to produce a mouse serum having specificity for the protein as representative example of the claimed genus of CAI antigen polypeptides. However, the disclosure that a full length cytotoxic CAI antigen can be used to produce mouse antiserum is insufficient to enable a "substantially noncytotoxic" full length CAI antigen, or at least 10-mer or 15-mer fragments thereof, which are "substantially noncytotoxic", immunogenic, *H. pylori*-specific and capable of serving as components of a therapeutic and prophylactic vaccine. Applicants further contend that several references submitted previously disclose various animal models for studying the effects of candidate vaccines on *H. pylori* infection in humans, and that nothing more than routine experimentation was required to determine which polypeptides and vaccines of the invention work therein. However, the mere existence of animal models in the art does not provide for 'substantially noncytotoxic' CAI, CT or HSP polypeptides and their 10-mer or 15-mer fragments which are *H. pylori*-specific, immunogenic and capable of serving as prophylactic or therapeutic vaccines against *H. pylori* infection. Given the art known unpredictability and the lack of establishment of a structure-function correlation within the instant specification for the claimed product(s), and the lack of

guidance or direction, production of the claimed substantially noncytotoxic polypeptide or its fragments having the required functions would have involved considerable quantity of undue experimentation that is complex and time consuming. The rejection stands.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office Action. The new rejection(s) is necessitated by Applicants' amendments to the claims and/or the base claim(s) and submission of new claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph

24) Claims 45, 47, 54, 56, 57, 59, 62, 63, 68, 70, 75, 76, 78 and 80 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 45, 54, 57, 62, 63, 70, 75 and 78, as amended, include the new limitation: "substantially noncytotoxic". Applicants state that this limitation is supported in the specification by the phrase "exhibits no functional contribution to toxicity, or substantially reduced functional contribution to toxicity". Applicants contend that the toxicity of the original phrase refers to cytotoxicity as stated at page 50, lines 24-37, wherein cytotoxicity as measured by vacuolizing activity on HeLa cells is shown to be associated with the presence of the CAI antigen. However, this assertion and this part of the specification showing the presence of "cytotoxicity" fail to provide descriptive support for a polypeptide comprising at least 10 contiguous amino acids of SEQ ID NO: 5, which is "substantially noncytotoxic". Furthermore, page 50 of the specification is unrelated to the cytotoxicity or non-cytotoxicity of the *H. pylori* CT or the heat shock protein The originally recited broad term "toxicity" was not defined or described within the instant specification, as originally filed, to be limited to 'cytotoxicity". Therefore, the limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or

invited to point to the page and line number in the specification where support for such a recitation can be found.

25) New claims 82, 83, 124 and 125 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. See paragraph 17 of the Office Action mailed 02/28/02 (paper no. 28) and paragraph 23 above for detailed explanation and reasoning.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

26) Claims 45, 47, 54, 56, 57, 59, 62, 63, 68, 70, 75, 76, 78 and 80 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 45, 54, 57, 62, 63, 70 and 78, are vague and indefinite in the recitation "substantially noncytotoxic", because it is unclear what is encompassed in this phrase. What degree of cytotoxicity or noncytotoxicity qualifies as 'substantial noncytotoxicity' is not understood.

(b) Claims 47, 68, 56, 59 and 80, which depend directly or indirectly, from one of the base claims identified above, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim(s).

Remarks

27) Claims 45, 47, 54, 56, 57, 59, 62, 63, 68, 70, 75, 76, 78, 80, 82, 83, 124 and 125 stand rejected. Claims 40, 41 and 72 are allowable. Claims 82 and 83 are objected to for being dependent on a non-elected claim.

28) The Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

29) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

30) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER